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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
114-154pct		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/CA 00/ 00770	30/06/2000	30/06/1999
Applicant		
IGT PHARMA INC.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. –

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

Continuation of Box I.2

Claims Nos.: 1(in part)-3(in part), 8(in part)- 12(in part), 14(in part)-19(in part)

Present claims 1 - 3, 8 - 12 and 14 - 19 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds according to one of the general formulas, wherein R1 and R2 are H, -COOH or -CH2-COOH, X is a carboxy group or protected carboxy group and Y is an amino group or protected amino group.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No
P[redacted]A 00/00770

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C229/50 C07C229/36 A61K31/195 A61K31/196 A61P25/28
C07C255/47 C07C255/42 C07C255/44 C07D235/02 C07D233/78

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 15099 A (NOVO NORDISK) 23 May 1996 (1996-05-23) page 4, line 12 -page 11, line 28; claims; examples 1,2	1-19
X	WO 98 51687 A (FUJISAWA PHARMACEUTICAL) 19 November 1998 (1998-11-19) page 50, preparation 47	19
X	WO 97 09346 A (CORTECH) 13 March 1997 (1997-03-13) example III	1-3,19
X	EP 0 515 681 A (FUJISAWA PHARMACEUTICAL) 2 December 1992 (1992-12-02) page 18, line 51 -page 20, line 23	1-3,16

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 October 2000	07/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Zervas, B

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 189 203 A (ABBOTT LABORATORIES) 30 July 1986 (1986-07-30) example 99 ---	16
X	EP 0 451 753 A (ASTA PHARMA) 16 October 1991 (1991-10-16) example 44 ---	14
X	ROGER M. PINDER ET AL.: "2-Aminoindan-2-carboxylic Acids. Potential Tyrosine Hydroxylase Inhibitors" JOURNAL OF MEDICINAL CHEMISTRY., vol. 14, no. 9, 1971, pages 892-893, XP002150544 AMERICAN CHEMICAL SOCIETY. WASHINGTON., US ISSN: 0022-2623 page 893; tables I,,II ---	1-3,8,9, 15,16
X	R. LOHMAR ET AL.: " alpha-Aminosäuren als Nukleophile Acyläquivalente, IV. Synthese Symmetrischer Ketone unter Verwendung von 2-Phenyl-2-oxazolin-5-on" CHEMISCHE BERICHTE, vol. 113, 1980, pages 3706-3715, XP002150545 WEINHEIM DE page 3714, line 3 - line 7 ---	16
X	RUDOLF KNORR ET AL.: "Azomethine, 1-Azaallyl-Anionen und Metastabile sek. Enamine" CHEMISCHE BERICHTE, vol. 113, 1980, pages 2462-2489, XP002150546 WEINHEIM DE page 2486, line 11 - line 18 ---	14
X	US 3 532 744 A (HORACE FLETCHER III ET AL.) 6 October 1970 (1970-10-06) claims; examples 1,3 ---	1-3,8,15
X	CHEMICAL ABSTRACTS, vol. 58, no. 13, 24 June 1963 (1963-06-24) Columbus, Ohio, US; abstract no. 13935g, A. B. MAUGER ET AL.: "Aryl 2-Haloalkyl Amines. XX. The Preparation and Propertiesof Some Bis(2-chlorethyl)aminoaryl-substituted Hydantoins and Related Amino Acids" XP002150547 abstract & BIOCHEM. PHARMACOL., vol. 11, 1962, pages 847-858, --- -/--	15

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INTERNATIONAL SEARCH REPORT

International Application No
P[redacted]A 00/00770

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 916 920 A (ELI LILLY) 29 June 1999 (1999-06-29) claims; examples	1,9-13
A	EP 0 807 621 A (LILLY INDUSTRIES) 19 November 1997 (1997-11-19) claims; examples	1,9-13

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/AU 00/00770

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9615099 A	23-05-1996	AU 1106195 A	06-06-1996
		AU 3839895 A	06-06-1996
		WO 9615100 A	23-05-1996
WO 9851687 A	19-11-1998	AU 6708298 A	11-05-1998
		WO 9816527 A	23-04-1998
WO 9709346 A	13-03-1997	US 5834431 A	10-11-1998
		AU 6856796 A	27-03-1997
EP 515681 A	02-12-1992	WO 9112266 A	22-08-1991
		US 5321032 A	14-06-1994
EP 189203 A	30-07-1986	US 4680284 A	14-07-1987
		AU 599581 B	26-07-1990
		AU 5274386 A	31-07-1986
		AU 6557490 A	31-01-1991
		AU 638093 B	17-06-1993
		AU 7028191 A	18-04-1991
		CA 1287445 A	06-08-1991
		DK 34086 A	24-07-1986
		ES 551249 D	01-11-1987
		ES 8800269 A	01-01-1988
		US 4837204 A	06-06-1989
		US 4845079 A	04-07-1989
		US 5091575 A	25-02-1992
		US 5214129 A	25-05-1993
		US 4725583 A	16-02-1988
		ZA 8600444 A	24-09-1986
		GR 860286 A	02-06-1986
		KR 9100405 B	25-01-1991
		AU 583971 B	11-05-1989
		AU 6759887 A	23-07-1987
		DK 20887 A	17-07-1988
		EP 0230266 A	29-07-1987
		IL 81233 A	21-06-1992
		JP 62234053 A	14-10-1987
		JP 62169753 A	25-07-1987
		KR 9102694 B	03-05-1991
		NZ 218937 A	27-03-1990
		AT 108456 T	15-07-1994
		AU 603080 B	08-11-1990
		AU 6759987 A	23-07-1987
		CA 1307289 A	08-09-1992
		DE 3750184 D	18-08-1994
		DE 3750184 T	10-11-1994
		DK 20987 A	17-07-1987
		EP 0229667 A	22-07-1987
		ES 2059313 T	16-11-1994
		IE 63602 B	17-05-1995
		IL 81234 A	06-09-1992
		IL 97441 A	06-09-1992
		JP 2525732 B	21-08-1996
		JP 62234052 A	14-10-1987
		JP 2101497 C	22-10-1996
		JP 6239811 A	30-08-1994
		JP 8000798 B	10-01-1996
		KR 9103348 B	28-05-1991

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PC[redacted] 00/00770

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 189203 A		NZ 218936 A	27-10-1989
EP 451753 A	16-10-1991	AU 7424491 A	17-10-1991
		CA 2040123 A	11-10-1991
		DE 4111249 A	06-02-1992
		FI 911698 A	11-10-1991
		HU 57788 A	30-12-1991
		JP 7112994 A	02-05-1995
		MC 2223 A	02-02-1993
		NO 911373 A	11-10-1991
		NO 924063 A	11-10-1991
		NO 924064 A	11-10-1991
		NZ 237443 A	25-11-1993
		PT 97294 A	31-01-1992
		US 5194644 A	16-03-1993
		US 5238955 A	24-08-1993
		ZA 9102630 A	29-01-1992
US 3532744 A	06-10-1970	NONE	
US 5916920 A	29-06-1999	AU 703093 B	18-03-1999
		AU 7731096 A	05-06-1997
		BR 9611521 A	29-06-1999
		CA 2237598 A	22-05-1997
		CN 1202103 A	16-12-1998
		EA 980380 A	29-10-1998
		EP 0774455 A	21-05-1997
		JP 2000500752 T	25-01-2000
		WO 9717950 A	22-05-1997
EP 807621 A	19-11-1997	CA 2204846 A	13-11-1997
		JP 10067723 A	10-03-1998
		US 5863947 A	26-01-1999

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 01 March 2001 (01.03.01)	
International application No. PCT/CA00/00770	**Applicant's or agent's file reference** 114-154pct
International filing date (day/month/year) 30 June 2000 (30.06.00)	**Priority date** (day/month/year) 30 June 1999 (30.06.99)
Applicant CURRY, Kenneth	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   18 January 2001 (18.01.01)

   [ ] in a notice effecting later election filed with the International Bureau on:

   _____

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer F. Baechler
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

REC'D 26 OCT 2001
PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
114-154PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA00/00770	30/06/2000	30/06/1999
International Patent Classification (IPC) or national classification and IPC C07C229/50		
Applicant IGT PHARMA INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 20 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18/01/2001	25.10.2001
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Zervas, B Telephone No. +31 70 340 3667

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA00/00770

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-4,7,10-24,26-41, 43,46,47	as originally filed			
5,6,8,9,25,42,44, 45	as received on	05/10/2001	with letter of	03/10/2001

Claims, No.:

1-17	as received on	05/10/2001	with letter of	03/10/2001

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   ☐ the language of publication of the international application (under Rule 48.3(b)).
   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☐ furnished subsequently to this Authority in written form.
   ☐ furnished subsequently to this Authority in computer readable form.
   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:
   ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
   see separate sheet

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 1-3,5,6,8-10,12-17 (all in part).

because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☒ the claims, or said claims Nos. 1-3,5,6,8-10,12-17(all in part) are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-3,5,6,8-10,12-17(all in part).

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims
	No:	Claims 1-17
Inventive step (IS)	Yes:	Claims

	No:	Claims	1-17
Industrial applicability (IA)	Yes:	Claims	1-7,12-17
	No:	Claims	8-11

2. Citations and explanations
see separate sheet

Re Item I

Basis of the report

The amendments of claims 1-and 12 - 17 have been considered as to go beyond the disclosure as originally filed (Rule 70(2)(c) PCT) for the following reason:

The Applicant has introduced a "disclaimer" into claims 1 and 12 - 17 in order to establish novelty over the prior art. Such a disclaimer is only allowable (which means it does not introduce new subject-matter), if exactly the compounds described in the prior art are disclaimed. The Applicant disclaims a whole range of compounds. Since this range of compounds does not correspond exactly to the compounds described in the prior art, the Applicant introduces new subject-matter into said claims. The amended claims 1 and 12 - 17 as presently worded relate to "a selection of compounds" (at least one of R1 and R2 is other than H) from the "range of compounds" of the original disclosure. However, the application as originally filed does not disclose any teaching (e. g. a preferred embodyment), which could be regarded as a basis for such a selection.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Present claims 1 - 3, 5, 6, 8 - 10 and 12 - 17 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful examination over the whole of the claimed scope is impossible.

The international search report has not been established for the part of claims 1-3which appear not to be supported and disclosed.

Consequently the examination has only been carried out for those parts of the claims which appear to be supported and disclosed (Art. 34(4)(a)(ii) PCT) and which have been searched (Rule 66.1(e) PCT), namely those parts relating to the compounds

according to one of the general formulas, wherein R1 and R2 are H, -COOH or -CH2-COOH, X is a carboxy group or protected carboxy group and Y is an amino group or protected amino group.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 96 15099 A
D2: WO 98 51687 A
D3: WO 97 09346 A
D4: EP 0 515 681 A
D5: EP 0 189 203 A
D6: EP 0 451 753 A
D7: J. Med. Chem. 14, 892-893 (1971)
D8: Chem. Ber. 113, 3706-3715 (1980)
D9: Chem. Ber. 113, 2462-2489 (1980)
D10: US 3 532 744 A
D11: CA 58: 13935g

1. Novelty

The present application does not satiesfy the criterion as set forth in Article 33(2) PCT, because the subject-matter of claims 1-19 is not novel.
The following documents D1 - D11 disclose compounds which fall within the scope of the present claims; for details see the following table:

table

document	passage	relevant to the claim(s)
D1	p.4, l.12 - p.11, l. 28; claims	1-17
D2	p.50, preparation 47	17

D3	example III	15,17
D4	p.18, l. 51 - p.20,l. 23	14
D5	example 99	14
D6	example-44	12
D7	p. 893, tables I,II	1-3,5,6,13,14
D8	p. 3714, l. 3 - l. 7	13
D9	p. 2486, l. 11 - l. 18	12
D10	examples 1,3; claims	13
D11	abstract	13

2. Inventive Step

Furthermore the present application does not satiesfy the criterion as set forth in Article 33(3) PCT, because the subject-matter of claims 1-17 is not inventive.
Since the subject-matter of claims 1-17 is not novel, it cannot be inventive either.

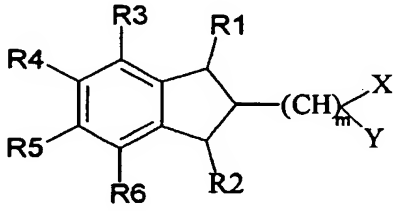
3. Industrial Applicability

Claims 8 -11 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion has been formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).
For the assessment of the present claims 8 - 11 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

The current pharmaceutical options for treating neurological disorders tend to be very general and non-specific in their actions in that, although they may reduce the clinical symptoms associated with a specific neurological disorder, they may also negatively impact normal function of the central nervous system of patients. Thus new cellular targets and drugs that are more specific in their actions require to be identified and developed and thus a need remains for chemical compounds that demonstrate specific binding characteristics towards mGluRs.

SUMMARY OF THE INVENTION

An object of the present invention is to provide 2-aminoindane analogs that demonstrate activity at the various metabotropic glutamate receptors. In accordance with an aspect of the invention, there is provided a compound of formula (I):



(I)

stereoisomers thereof, or pharmaceutically acceptable salts or hydrates thereof, wherein:

R1, and **R2** are selected from the group comprising:

1) H; or:

2) an acidic group selected from the group comprising carboxy, phosphono, phosphino, sulfono, sulfino, borono, tetrazol, isoxazol, -$(CH_2)_n$-carboxy, -$(CH_2)_n$-phosphono, -$(CH_2)_n$-phosphino, -$(CH_2)_n$-sulfono,-$(CH_2)_n$-sulfino, -$(CH_2)_n$-borono, -$(CH_2)_n$-tetrazol, and -$(CH_2)_n$-isoxazol, where n = 1, 2, 3, 4, 5, or 6; or:

X is an acidic group selected from the group comprising carboxy, phosphono, phosphino, sulfono, sulfino, borono, tetrazol, isoxazol.

Y is a basic group selected from the group comprising 1° amino, 2° amino, 3° amino, quaternary ammonium salts, aliphatic 1° amino, aliphatic 2° amino, aliphatic 3° amino, aliphatic quaternary ammonium salts, aromatic 1° amino, aromatic 2° amino, aromatic 3° amino, aromatic quaternary ammonium salts, imidazol, guanidino, boronoamino, allyl, urea, thiourea ;

m is 0, 1.

R3, R4, R5, R6 are independently H, nitro, amino, halogen, tritium, trifluoromethyl, trifluoroacetyl, sulfo, carboxy, carbamoyl, sulfamoyl or acceptable esters thereof;

or a salt thereof with a pharmaceutically acceptable acid or base.

DETAILED DESCRIPTION OF THE INVENTION

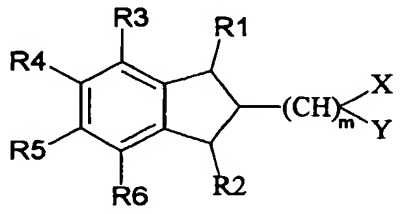
The terms and abbreviations used in the instant examples have their normal meanings unless otherwise designated. For example "°C" refers to degrees Celsius; "N" refers to normal or normality; "mmol" refers to millimole or millimoles; "g" refers to gram or grams; "ml" means milliliter or milliliters; "M" refers to molar or molarity; "*p*-" refers to para, "MS" refers to mass spectrometry; "IR" refers to infrared spectroscopy; and "NMR" refers to nuclear magnetic resonance spectroscopy.

As would be understood by the skilled artisan, throughout the synthesis of the compounds of Formula I it may be necessary to employ an amino-protecting group or a carboxy-protecting group in order to reversibly preserve a reactively susceptible amino or carboxy functionality while reacting other functional groups on the compound.

Examples of such amino-protecting groups include formyl, trityl, phthalimido, trichloroacetyl, chloroacetyl, bromoacetyl, iodoacetyl, and urethane-type blocking groups such as benzyloxycarbonyl, 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxycarbonyl,

t-butyldimethylsilyl, phenacyl, 2,2,2-trichloroethyl, β-(di(n-butyl)methylsilyl)ethyl, *p*-toluenesulfonylethyl, 4-nitrobenzylsulfonylethyl, allyl, cinnamyl, 1-(trimethylsilylmethyl)prop-1-en-3-yl and like moieties. Preferred carboxy-protecting groups are allyl, benzyl and *t*-butyl. Further examples of these groups are found in E. Haslam, supra, at Chapter 5; and T. W. Greene and P. G. M. Wuts, supra, at Chapter 5.

The present invention provides a compound of the formula I:



(I)

Stereoisomers thereof, or pharmaceutically acceptable salts or hydrates thereof, wherein:

R1, and **R2** are selected from the group comprising:

1) H

2) an acidic group selected from the group comprising carboxy, phosphono, phosphino, sulfono, sulfino, borono, tetrazol, isoxazol, -$(CH_2)_n$-carboxy, -$(CH_2)_n$-phosphono, -$(CH_2)_n$-phosphino, -$(CH_2)_n$-sulfono,-$(CH_2)_n$-sulfino, -$(CH_2)_n$-borono, -$(CH_2)_n$-tetrazol, and -$(CH_2)_n$-isoxazol, where n = 1, 2, 3, 4, 5, or 6; or

X is an acidic group selected from the group comprising carboxy, phosphono, phosphino, sulfono, sulfino, borono, tetrazol, isoxazol.

Y is a basic group selected from the group comprising 1° amino, 2° amino, 3° amino, quaternary ammonium salts, aliphatic 1° amino, aliphatic 2° amino, aliphatic 3° amino, aliphatic quaternary ammonium salts, aromatic 1° amino, aromatic 2° amino, aromatic 3°

amino, aromatic quaternary ammonium salts, imidazol, guanidino, boronoamino, allyl, urea, thiourea ;

m is 0, 1.

R3, R4, R5, R6 are independently H, nitro, amino, halogen, tritium, trifluoromethyl, trifluoroacetyl, sulfo, carboxy, carbamoyl, sulfamoyl or pharmaceutically acceptable esters or salts thereof,

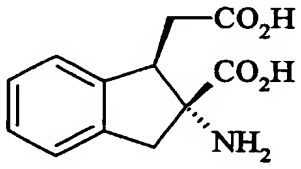
In one embodiment of the present invention a compound of formula (I) is provided, wherein:

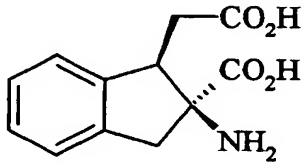
R1 is CO_2H, or CH_2CO_2H; **R2** is H; **X** is CO_2H; and **Y** is NH_2

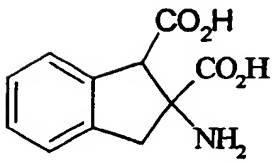
In another embodiment of the present invention a compound of formula (I) is provided, wherein:

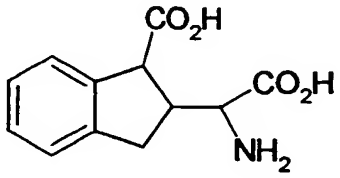
R1 is H; **R2** is CO_2H or CH_2CO_2H; **X** is CO_2H; and **Y** is NH_2

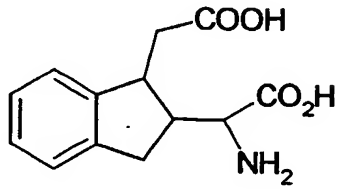
Compounds of the present invention include, but are not limited to the following exemplary molecules:











1992; Tanabe *et al.*, Neuron 8, 169-179, 1992, and J. Neurochem. 63, 2038-2047, 1993). They are maintained at 37 °C in a humidified 5% CO_2 incubator in Dubecco's Modified Eagle Medium (DMEM) containing a reduced concentration of (S)-glutamine (2mM) and are supplemented with 1% proline, penicillin (100 U/mL), streptomycin (100 mg/mL) and 10% dialyzed fetal calf serum (all GIBCO, Paisley). Two days before assay 1.8×10^6 cells are evenly distributed into the wells of 24 well plates.

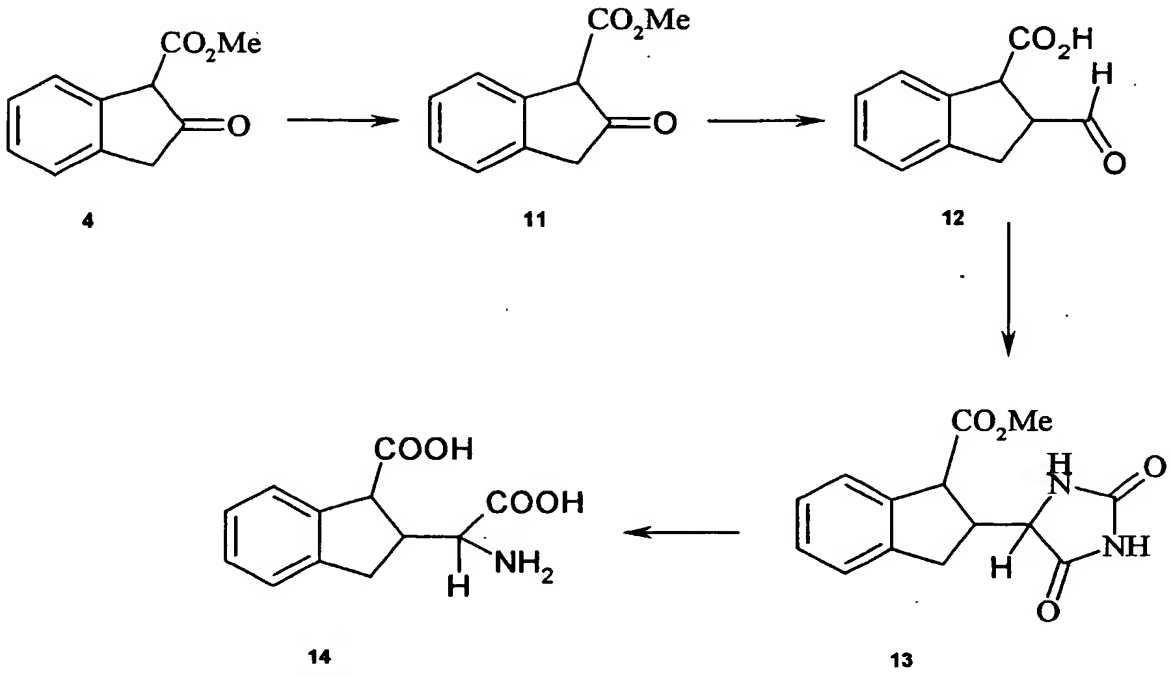
Phosphatidylinositol (PI) hydrolysis can be measured as described previously (Hayashi *et al.*, Nature 366, 687-690,1992, and J. Neuroscience 14, 3370-3377, 1994). Briefly, the cells are labeled with [^{3}H]inositol (2μ Ci/mL) 24 h prior to the assay. For agonist assays, the cells are incubated with test compound dissolved in phosphate-buffered saline (PBS)-LiCl for 20 min, and agonist activity is determined from the level of ^{3}H-labeled mono-, bis- and tris-inositol phosphates generated, as measured following ion-exchange chromatography, compared with the level generated in the absence of the test compound. For antagonist assays, the cells are preincubated with ligand dissolved in PBS-LiCl for 20 min prior to incubation with test compound and 10 μ M (S)-Glu for 20 min. The antagonist activity is then determined as the inhibitory effect of the (S)-Glu mediated response.

The assay of cyclic AMP formation can be performed as described previously (Hayashi *et al.*, 1992, 1994). Briefly, the cells are incubated for 10 min in PBS containing test coumpound and 10 μ M forskolin and 1 mM 3-isobutyl-1-methylxanthine (IBMX) (both Sigma, St. Louis, MO, USA). The agonist activity is then determined as the inhibitory effect on the forskolin-induced cyclic AMP formation. For antagonist assay, the cells are preincubated with ligand dissolved in PBS containing 1 mM IBMX for 20 min prior to a 10 min incubation in PBS containing test compound, 20 μ M(mGlu2) or 50 μ M (mGlu4a) (S)-Glu, 10 μ M forskolin and 1 mM IBMX. The antagonist activity is then determined as the potentiating effect on the forskolin-induced cyclic AMP formation.

In Vivo Testing:

In *vivo* testing for demonstration of the pharmacological activity of certain compounds on representative mGlu receptor subtypes can be performed using Sprague Dawley rat tissues.

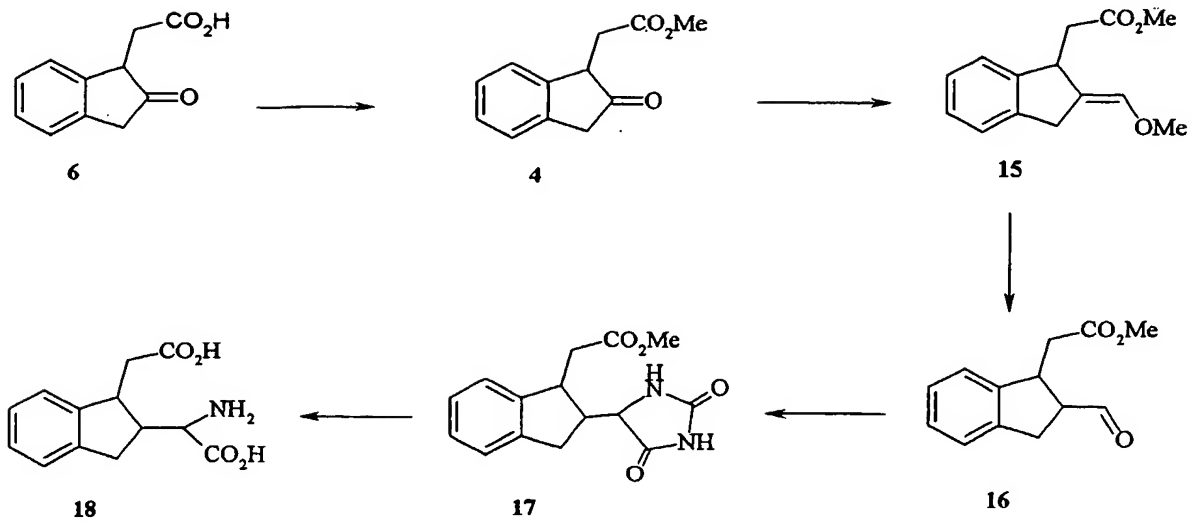
Example 3:



Preparation of intermediate Compound (**11**):

Sodium bis(trimethylsilyl)amide was added to a stirred solution of (methoxymethyl)triphenylphosphonium chloride (9.51 g) in dry THF (80 mL) at 0 °C under N_2. The resulting solution was stirred at 0 °C for 35 min and then 4.31g of compound **4** was added a solution in THF (40 mL) over 10 min. The resulting mixture was stirred at 0 °C for 2 h and at room temperature for 1 h. The reaction was quenched with water (30 mL), and the mixture was partitioned between brine (200 mL) and EtOAc (200 mL). Ogranic extracts were washed with brine (2x150 mL) and the combined aqueous phases were extracted with EtOAc (3 x 150 mL). The combined organic extracts were dried and concentrated. The crude product was purified by column chromatography (hexanes: EtOac, 9:1) to yield 3.11 g (62.8%) of compound (**11**).

Preparation of intermediate Compound (**12**):



Preparation of intermediate compound (**4**):

Compound **4** can either be prepared as shown in example 1, in an alternative manner compound **4** can be prepared form compound **6** (from example 1) as shown below:

The ketoacid **6** (3.5g) was dissolved in 50 mL of methanol, saturated with HCl gas and refluxed for 2 h. The resulting solution was cooled, evaporated to dryness and the residue was taken up in 100 mL of diethyl ether. The ethereal extracts were washed with saturated sodium bicarbonate solution, dried over magnesium sulphate and evaporated to give crude **4**. The residue was purified by flash chromatography on silica (ethyl acetate:hexanes 1:9-3:7) to yield 3.1 g (84%) of pure compound **4**.

Preparation of intermediate compound (**15**)

Sodium bis(trimethylsilyl)amide (17.9mL) was added to a stirred suspension of (methoxy methyl)triphenylphosphonium chloride (6.4g) in dry THF (60 mL) at 0 °C under N_2. The resulting red mixture was stirred at 0 °C for 35 minutes and a solution of compound **4** (3.1g) in dry THF (40 mL) added over 10 minutes. The mixture was stirred at 0 °C for 2 h and at room temperature for 1 h. The reaction mixture was quenched with 20 mL of water and partitioned between brine (100 mL) and EtOAc (100 mL). The crude product was purified by column chromatography (hexanes: EtOAc, 9: 1) to obtain 3.01g (85%) of compound **15**.

Preparation of intermediate compound (**16**)

To a stirred solution of compound **15** in pyridine (0.4 mL) and $CHCl_3$ (275 mL) at 0 °C, was added 0.3 mL of trimethylsilyl iodide under N2. The resulting mixture was stirred for 1.5 h and a further 0.3 mL of trimethylsilyl iodide added. The mixture was stirred for 40 min and quenched with 80 mL of ice cold $NaHCO_3$ solution. The mixture was stirred for 10 min then poured into brine and extracted with ethyl acetate (2 x 200 mL). The resulting solution was washed with brine, dried over MgSO4 and evaporated to give compound **16** as a gum. The material was purified by column chromatography (hexanes: EtOAc 80:10-85:15) to yield 2.21g (76.1%) of pure compound **16**.

Preparation of intermediate compound (**17**)

The aldehyde **16** was dissolved in 25 mL of 1:1 EtOH:water along with 1.5 g KCN and 3g $(NH_4)_2CO_3$. The mixture was placed in a sealed pressure vessel and heated to 85 °C for 18 h. The resulting dark mixture was carefully acidified with 6 M HCl and evaporated to dryness. The residue was extracted with EtOH, filtered and evaporated to give the crude hydantoin **17**, which was used without further purification.

Preparation of intermediate compound (**18**)

The crude hydantoin **17** was taken up in 20 mL of 2 M NaOH and sealed in a pressure vessel. The mixture was heated to 140 °C for 4 h and then cooled to room temperature. The mixture was acidified with 6 M HCl and evaporated to dryness. The residue was taken up in EtOH and filtered. The amino acid was obtained by precipitation with propylene oxide and filtration to give the amino acid **18** as a mixture of *cis* and *trans* isomers.

***In Vivo* Testing of Exemplary Compounds:**

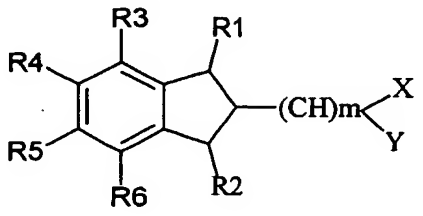
Cyclic AMP assay:

Rationale:

Group II/III metabotropic glutamate receptors (mGluRs) are negatively coupled to adenylate cyclase, and agonists of these receptors lead to a decrease in intracellular cyclic AMP accumulation.

EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY PREVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A compound having structural formula (I):



(I)

stereoisomers thereof, or pharmaceutically acceptable salts or hydrates thereof, wherein:

R1, and **R2** are selected from the group comprising:

(i) H

(ii) an acidic group selected from the group comprising carboxy, phosphono, phosphino, sulfono, sulfino, borono, tetrazol, isoxazol, -$(CH_2)_n$-carboxy, -$(CH_2)_n$-phosphono, -$(CH_2)_n$-phosphino, -$(CH_2)_n$-sulfono,-$(CH_2)_n$-sulfino, -$(CH_2)_n$-borono, -$(CH_2)_n$-tetrazol, and -$(CH_2)_n$-isoxazol, where n =1, 2, 3, 4, 5, or 6;

X is an acidic group selected from the group comprising carboxy, phosphono, phosphino, sulfono, sulfino, borono, tetrazol, isoxazol.

Y is a basic group selected from the group comprising 1° amino, 2° amino, 3° amino, quaternary ammonium salts, aliphatic 1° amino, aliphatic 2° amino, aliphatic 3° amino, aliphatic quaternary ammonium salts, aromatic 1° amino, aromatic 2°

amino, aromatic 3° amino, aromatic quaternary ammonium salts, imidazol, guanidino, boronoamino, allyl, urea, thiourea ;

m is 0, 1.

R4, R5, R6, R7 are independently H, nitro, amino, halogen, tritium, trifluoromethyl, trifluoroacetyl, sulfo, carboxy, carbamoyl, sulfamoyl, or an acceptable ester thereof.

2. A compound as claimed in claim 1, wherein **R1** can be H, CO_2H, CH_2CO_2H.

3. A compound as claimed in claim 1, wherein **R2** can be H, CO_2H, CH_2CO_2H.

4. A compound according to claim 1, wherein, m = 0, **R1** is CH_2COOH, **R2** = **R3** = **R4** = **R5** = **R6** = H, X is COOH, Y is NH_2.

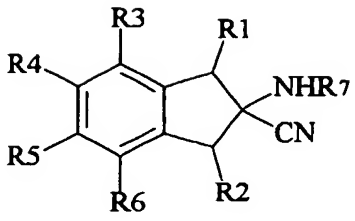
5. A compound according to claim 1, wherein, m = 0, **R1** is COOH, **R2** = **R3** = **R4** = **R5** = **R6** = H, X is COOH, Y is NH_2.

6. A compound according to claim 1, wherein, m = 1, **R1** is COOH, **R2** = **R3** = **R4** = **R5** = **R6** = H, X is COOH, Y is NH_2.

7. A compound according to claim 1, wherein, m = 1, **R1** is CH_2COOH, **R2** = **R3** = **R4** = **R5** = **R6** = H, X is COOH, Y is NH_2.

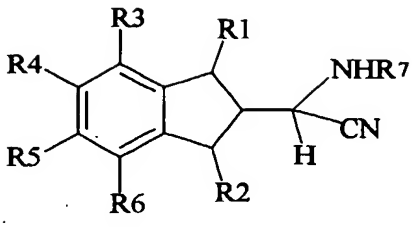
8. A process for the preparation of a compound of Formula I, or a pharmaceutically acceptable metabolically-labile ester or amide thereof, or a pharmaceutically acceptable salt thereof, which comprises:

a) hydrolyzing a compound of formula (IIa) or (IIb):



(IIa)

or



(IIb)

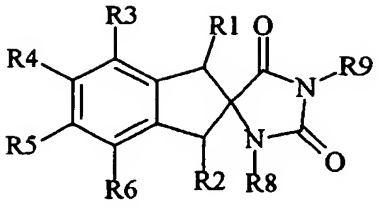
wherein: **R1**, and **R2** are selected from the group comprising:

i) H

ii) an acidic group selected from the group comprising carboxy, phosphono, phosphino, sulfono, sulfino, borono, tetrazol, isoxazol, -$(CH_2)_n$-carboxy, -$(CH_2)_n$-phosphono, -$(CH_2)_n$-phosphino, -$(CH_2)_n$-sulfono,-$(CH_2)_n$-sulfino, -$(CH_2)_n$-borono, -$(CH_2)_n$-tetrazol, and -$(CH_2)_n$-isoxazol, wherein n =1, 2, 3, 4, 5, or 6;

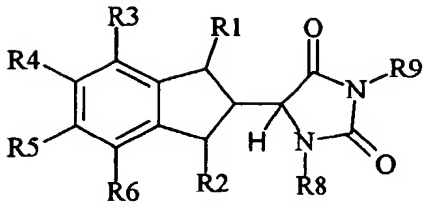
R3, **R4**, **R5** and **R6** are independently H, nitro, amino, halogen, tritium, trifluoromethyl, trifluoroacetyl, sulfo, carboxy, carbamoyl, sulfamoyl, or pharmaceutically acceptable ester or salt thereof, **R7** is a hydrogen atom or an acyl group. Preferred functional groups for **R7** are hydrogen and (2-6C) alkanoyl groups, such as acetyl; or

b) hydrolyzing a compound of formula (IIIa) or (IIIb):



(IIIa)

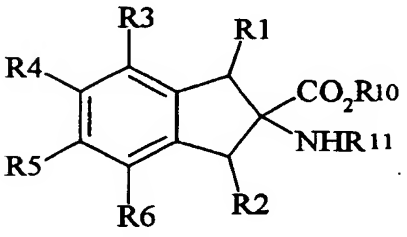
or



(IIIb)

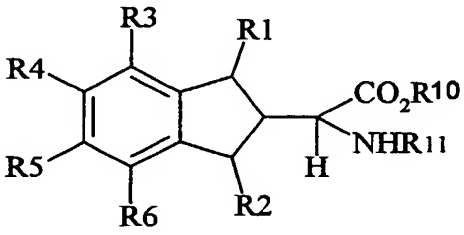
wherein: **R1**, **R2**, **R3**, **R4**, **R5** and **R6** are as defined above, **R8** and **R9** are each independently represent a hydrogen atom, a (C_2-C_6) alkanoyl group, a (C_1-C_4) alkyl group, a (C_3-C_4) alkenyl group or a phenyl (C_1-C_4) alkyl group wherein the phenyl is unsubstituted or substituted by halogen, (C_1-C_4) alkyl or (C_1-C_4) alkoxy, or a salt thereof; or

c) deprotecting a compound of formula (IVa) or (IV b):



(IVa)

or



(IVb)

wherein: **R1**, **R2**, **R3**, **R4**, **R5** and **R6** are as defined above and **R10** is a hydrogen atom or a carboxyl protecting group, or a salt thereof, and **R11** represents a hydrogen atom or a nitrogen protecting group;

whereafter, if necessary and/or desired, the following steps are carried out:

i) resolving the compound of Formula I;

ii) converting the compound of Formula I into a non-toxic metabolically labile ester or amide thereof and/or;

iii) converting the compound of Formula I or a non-toxic metabolically labile ester or amide thereof into a pharmaceutically acceptable salt thereof.

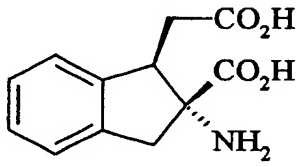
9. A pharmaceutical formulation, which comprises a compound as claimed in claim 1 and a pharmaceutically acceptable carrier, diluent or excipient.

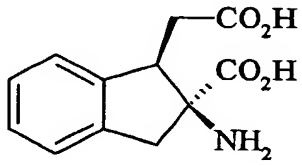
10. A use of the compound of structural formula (I) as claimed in claim 1, in modulating one or more metabotropic glutamate receptor functions in warm blooded mammals, wherein said use comprises administering an effective amount of a compound of formula (I).

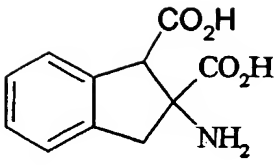
11. A use of the compound of structural formula (I) as claimed in claim 1, in treating a neurological disease or disorder selected from the group comprising: cerebral deficits subsequent to cardiac bypass surgery and grafting, cerebral ischemia, stroke, cardiac arrest, spinal cord trauma, head trauma, perinatal hypoxia, and hypoglycemic neuronal damage, Alzheimer's disease, Huntington's Chorea, amyotrophic lateral sclerosis, AIDS-induced dementia, ocular damage, retinopathy, cognitive disorders, idiopathic and drug-induced Parkinson's disease, muscular spasms, convulsions, migraine headaches, urinary incontinence, psychosis, drug tolerance, withdrawal, and cessation (i.e. opiates, benzodiazepines, nicotine, cocaine, or ethanol), smoking cessation, anxiety and related disorders (e.g. panic attack), emesis, brain edema, chronic pain, sleep disorders, Tourette's syndrome, attention deficit disorder, and tardive dyskinesia, wherein said use comprises administering an effective amount of a compound of formula (I).

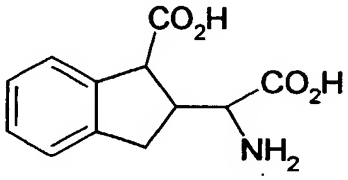
12. A use of the compound of structural formula (I), as claimed in claim 1, in treating a psychiatric disease or disorder selected from the group comprising: schizophrenia, anxiety and related disorders (e.g. panic attack), depression, bipolar disorders, psychosis, and obsessive compulsive disorders, wherein said use comprises administering an effective amount of a compound of formula (I).

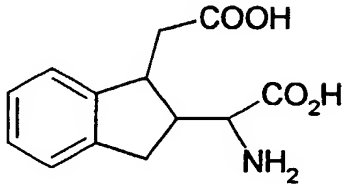
13. The use according to any one of claims 7, 8 and 9 wherein said compound is selected from the group of compounds comprising :



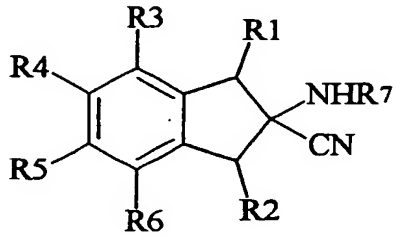








14. A compound of formula (IIa):



(IIa)

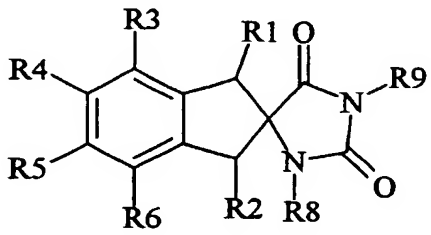
wherein: wherein: **R1**, and **R2** can each separately be selected from the group consisting of:

i) H

ii) an acidic group selected from the group comprising carboxy, phosphono, phosphino, sulfono, sulfino, borono, tetrazol, isoxazol, -$(CH_2)_n$-carboxy, -$(CH_2)_n$-phosphono, -$(CH_2)_n$-phosphino, -$(CH_2)_n$-sulfono,-$(CH_2)_n$-sulfino, -$(CH_2)_n$-borono, -$(CH_2)_n$-tetrazol, and -$(CH_2)_n$-isoxazol, where n =1, 2, 3, 4, 5, or 6;

R3, **R4**, **R5** and **R6** are independently H, nitro, amino, halogen, tritium, trifluoromethyl, trifluoroacetyl, sulfo, carboxy, carbamoyl, sulfamoyl, or pharmaceutically acceptable ester or salt thereof, **R7** is a hydrogen atom or an acyl group. Preferred functional groups for **R7** are hydrogen and (2-6C) alkanoyl groups, such as acetyl; or

15. A compound of formula (IIIa):



(IIIa)

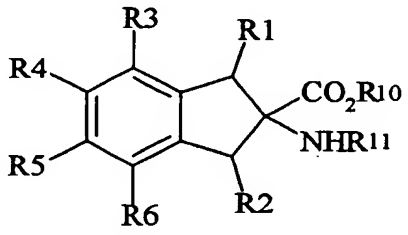
wherein: wherein: **R1**, and **R2** can each separately be selected from the group consisting of:

i) H

ii) an acidic group selected from the group comprising carboxy, phosphono, phosphino, sulfono, sulfino, borono, tetrazol, isoxazol, -$(CH_2)_n$-carboxy, -$(CH_2)_n$-phosphono, -$(CH_2)_n$-phosphino, -$(CH_2)_n$-sulfono,-$(CH_2)_n$-sulfino, -$(CH_2)_n$-borono, -$(CH_2)_n$-tetrazol, and -$(CH_2)_n$-isoxazol, wherein n =1, 2, 3, 4, 5, or 6;

R3, **R4**, **R5** and **R6** are independently H, nitro, amino, halogen, tritium, trifluoromethyl, trifluoroacetyl, sulfo, carboxy, carbamoyl, sulfamoyl, or pharmaceutically acceptable ester or salt thereof; **R8** and **R9** are each independently represent a hydrogen atom, a (C_2-C_6) alkanoyl group, a (C_1-C_4) alkyl group, a (C_3-C_4) alkenyl group or a phenyl (C_1-C_4) alkyl group wherein the phenyl is unsubstituted or substituted by halogen, (C_1-C_4) alkyl or (C_1-C_4) alkoxy, or a salt thereof or:

16. A compound of formula (IVa):



(IVa)

wherein: wherein: wherein: **R1**, and **R2** can each separately be selected from the group consisting of:

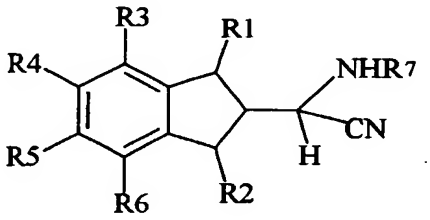
i) H

ii) an acidic group selected from the group comprising carboxy, phosphono, phosphino, sulfono, sulfino, borono, tetrazol, isoxazol, -$(CH_2)_n$-carboxy, -$(CH_2)_n$-phosphono, -$(CH_2)_n$-phosphino, -

$(CH_2)_n$-sulfono,-$(CH_2)_n$-sulfino, -$(CH_2)_n$-borono, -$(CH_2)_n$-tetrazol, and -$(CH_2)_n$-isoxazol, wherein n =1, 2, 3, 4, 5, or 6;

R3, **R4**, **R5** and **R6** are independently H, nitro, amino, halogen, tritium, trifluoromethyl, trifluoroacetyl, sulfo, carboxy, carbamoyl, sulfamoyl, or pharmaceutically acceptable ester or salt thereof; **R10** is a hydrogen atom or a carboxyl protecting group, or a salt thereof, and **R11** is a hydrogen atom or a nitrogen protecting group.

17. A compound of formula (IIb):



(IIb)

wherein: wherein: wherein: **R1**, and **R2** can each separately be selected from the group consisting of:

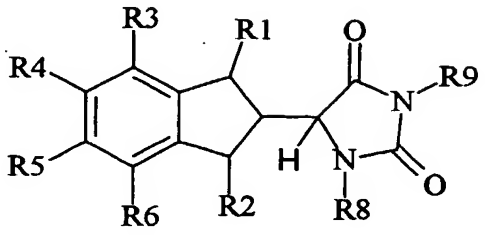
i) H

ii) an acidic group selected from the group comprising carboxy, phosphono, phosphino, sulfono, sulfino, borono, tetrazol, isoxazol, -$(CH_2)_n$-carboxy, -$(CH_2)_n$-phosphono, -$(CH_2)_n$-phosphino, -$(CH_2)_n$-sulfono,-$(CH_2)_n$-sulfino, -$(CH_2)_n$-borono, -$(CH_2)_n$-tetrazol, and -$(CH_2)_n$-isoxazol, wherein n =1, 2, 3, 4, 5, or 6;

R3, **R4**, **R5** and **R6** are independently H, nitro, amino, halogen, tritium, trifluoromethyl, trifluoroacetyl, sulfo, carboxy, carbamoyl, sulfamoyl, or pharmaceutically acceptable ester or salt thereof; **R7** is a hydrogen atom or an acyl

group. Preferred functional groups for **R7** are hydrogen and (2-6C) alkanoyl groups, such as acetyl.

18. A compound of formula (IIIb):



(IIIb)

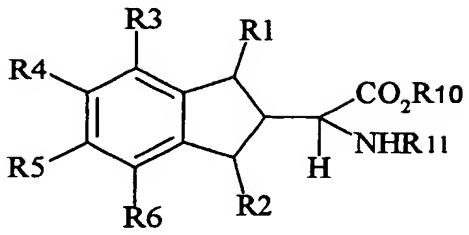
wherein: wherein: wherein: **R1**, and **R2** can each separately be selected from the group consisting of:

i) H

ii) an acidic group selected from the group comprising carboxy, phosphono, phosphino, sulfono, sulfino, borono, tetrazol, isoxazol, -$(CH_2)_n$-carboxy, -$(CH_2)_n$-phosphono, -$(CH_2)_n$-phosphino, -$(CH_2)_n$-sulfono,-$(CH_2)_n$-sulfino, -$(CH_2)_n$-borono, -$(CH_2)_n$-tetrazol, and -$(CH_2)_n$-isoxazol, wherein n =1, 2, 3, 4, 5, or 6;

R3, **R4**, **R5** and **R6** are independently H, nitro, amino, halogen, tritium, trifluoromethyl, trifluoroacetyl, sulfo, carboxy, carbamoyl, sulfamoyl, or pharmaceutically acceptable ester or salt thereof; **R8** and **R9** are each independently represent a hydrogen atom, a (2-6C) alkanoyl group, a (1-4C) alkyl group, a (3-4C) alkenyl group or a phenyl (1-4C) alkyl group wherein the phenyl is unsubstituted or substituted by halogen, (1-4C) alkyl or (1-4C) alkoxy, or a salt thereof or:

19. A compound of formula (IVb):



(IVb)

wherein: wherein: wherein: **R1**, and **R2** can each separately be selected from the group consisting of:

i) H

ii) an acidic group selected from the group comprising carboxy, phosphono, phosphino, sulfono, sulfino, borono, tetrazol, isoxazol, -$(CH_2)_n$-carboxy, -$(CH_2)_n$-phosphono, -$(CH_2)_n$-phosphino, -$(CH_2)_n$-sulfono,-$(CH_2)_n$-sulfino, -$(CH_2)_n$-borono, -$(CH_2)_n$-tetrazol, and -$(CH_2)_n$-isoxazol, wherein n =1, 2, 3, 4, 5, or 6;

R3, **R4**, **R5** and **R6** are independently H, nitro, amino, halogen, tritium, trifluoromethyl, trifluoroacetyl, sulfo, carboxy, carbamoyl, sulfamoyl, or pharmaceutically acceptable ester or salt thereof; **R10** is a hydrogen atom or a carboxyl protecting group or a salt thereof, and **R11** is a hydrogen atom or a nitrogen protecting group.